REMARKS

In the Final Action dated July 10, 2003, claims 18-19 are pending and are under consideration. Claims 18-19 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Green et al. (The Veterinary Record, May 2, 1987) and Geresi et al. (Ann. Immuno. Hung 25:37-40, 1985) in view of Wu et al. (J. Immunol. 148:1519-1525, 1992) and Gluck et al. (U.S. Patent No. 5,879,685).

This Response addresses the Examiner's rejection. Accordingly, the present application is in condition for allowance or at least in better condition for appeal. Favorable consideration of all pending claims is therefore respectfully requested.

In raising the §103(a) rejection, the Examiner contends that Green et al. teach a formulation of a multivalent clostridial vaccine for the purpose of stimulating a protective immune response against multiple strains and species of Clostridia. The Examiner admits that Green et al. fail to teach the use of a viral antigen in the multivalent clostridial vaccine. The Examiner also contends that Geresi et al. teach a freeze-dried vaccine composition containing *C. perfringens* antigens (C-D-type toxins) and another antigen. The Examiner admits that Geresi et al. fail to teach the use of an adjuvant. Furthermore, the Examiner contends that Wu et al. disclose that a recombinant HIV envelope protein, when used in combination with a saponin adjuvant, produced a higher titer of antibodies in test mice compared to control mice vaccinated only with an alum-adsorbed HIV envelope protein. Moreover, the Examiner contends that Gluck et al. teach an immunostimulating combination of influenza virus and *Clostridium tetani*.

In the Examiner's opinion, it would have been *prima facie* obvious to one skilled in the art, at the time the invention was made, to modify or combine the compositions of Green et al. and Geresi et al. by including a respiratory virus taught by Gluck et al. and the saponin

adjuvant of Wu et al., allegedly because all of the references are directed to the formulation of vaccines for enhanced immune response.

The Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where the suggestion or motivation to do so is found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The Examiner contends that, in this case, the motivation of combining immunogenic compositions containing Clostridium species and respiratory virus is derived from the teachings of Gluck et al. Gluck et al. teach an immunostimulating combination of influenza virus and *Clostridium tetani*. The Examiner also contends that use of different adjuvants in vaccines, e.g., saponin, is well known in the art, as disclosed in Wu et al. Therefore, the Examiner concludes that, in the absence of unexpected results, Green et al. and Geresi et al., in view of Gluck et al. and Wu et al., render the instantly claimed vaccines obvious.

In response, Applicants respectfully submit that a principal feature of the present invention resides in the unique recognition that the water-soluble adjuvant, saponin, can be used in place of a depot adjuvant, e.g., aluminum compounds, in multicomponent clostridial vaccines for cattle. As described in the present specification at page 1, lines 32-37, clostridial toxoids are soluble proteins of relatively low antigenicity and, traditionally, poor stability. Thus, clostridial vaccines require adjuvants in order to increase antigenic potency and to enhance stability. Typically, aluminum compounds are used as adjuvants, which are capable of adsorbing and/or precipitating clostridial toxoids, as well as retaining the toxoids at the injection site. However, as described in the specification at page 1, lines 35-37, aluminum compound-based adjuvants often

provoke severe persistent local reactions, such as granulomas, abscesses and scarring, when injected subcutaneously or intramuscularly. It has been surprisingly found by the present inventors that stable, potent, multicomponent clostridial vaccines can be made with rapidly dispersed, soluble adjuvants such as saponins, and without the use of depot adjuvants.

To favorably advance the prosecution of the present application and to further delineate the features of the present invention, Applicants have amended independent claim 18 to add "wherein said vaccine composition does not contain an aluminium compound-based depot adjuvant". Applicants respectfully submit that the vaccine compositions, as presently claimed, are not rendered obvious based on the combination of the cited references.

In the first instance, Applicants respectfully submit that none of the cited references, taken alone or in combination, provide any suggestion or motivation to those skilled in the art to combine the respective teachings of the references. Green et al. teach a vaccine composition which includes an aluminum hydroxide adjuvant. Applicants submit that aluminum compounds are specifically described in the present application as being unsuitable adjuvants for vaccine compositions. Thus, Green et al. provide a clear teaching away from the composition of the present invention.

As to Geresi et al., the Examiner admits that this reference fails to teach the use of an adjuvant, let alone a soluble adjuvant such as a saponin, which is employed in the presently claimed vaccine composition.

Gluck et al. may have taught a combination of influenza virus and *Clostridium tetani*. However, Applicants respectfully submit that Gluck et al. do not teach or even suggest the use of saponin as an adjuvant in the vaccine.

Regarding Wu et al., this reference apparently discloses the use of a saponin adjuvant in association with a recombinant HIV envelope protein. However, Applicants respectfully submit that Wu et al. clearly show that the saponin adjuvant, when used alone without alum, did not have any adjuvant effect. In this regard, Applicants respectfully direct the Examiner's attention to Figure 2 at page 1521 of Wu et al., where Wu et al. demonstrated that the immunostimulating effect of the saponin adjuvant was observed only when the saponin was used in combination with alum. Therefore, Wu et al. would not have provided any motivation to those skilled in the art to make a vaccine composition with a saponin and without an aluminium compound based adjuvant, as presently claimed.

Clearly, none of the cited references, taken alone or in combination, provide any teaching or suggestion that would have motivated those skilled in the art to combine the respective teachings of the references in order to arrive at the presently claimed vaccine compositions.

Furthermore, Applicants respectfully submit that the results achieved with the presently claimed vaccine compositions are unexpected. In particular, those skilled in the art would not have reasonably expected that the use of soluble adjuvants that are readily dispersed from the injection site and have no depot effect, such as saponin, in a multicomponent clostridial vaccine, would be successful in enhancing the potency of the clostridial antigens.

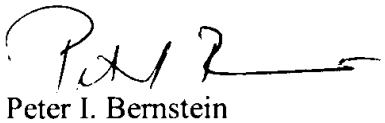
In this regard, Applicants respectfully direct the Examiner's attention to the specification, at pages 13-18, where multicomponent clostridial vaccines containing a saponin adjuvant were compared to vaccines containing the same clostridial components but with aluminium hybroxide gel as adjuvant. As described at pages 14-15, while the $Al(OH)_3$ gel-adjuvanted vaccines provoked chronic local reactions (such as swelling) for an extended period

(e.g., 6 weeks), the saponin-adjuvanted vaccine only induced transient reactions at the injection sites that disappeared quickly after a few days. In addition, a saponin-adjuvanted vaccine containing seven clostridial antigens induced stronger antibody response against *C. chauvoei* than a vaccine containing the same clostridial antigens and aluminium hybroxide gel as adjuvant.

Accordingly, Applicants respectfully submit that there is no suggestion in the cited references to combine the separate features of Green et al., Geresi et al., Wu et al. or Gluck et al. in order to achieve the claimed invention. In addition, even assuming, *pro arguendo*, that there was a suggestion to combine the respective teachings of the cited references, the results achieved by the claimed vaccines are still unexpected. Therefore, Applicants respectfully submit that the rejection of claims 18-19 under 35 U.S.C. §103(a) is overcome and withdrawal thereof is respectfully requested.

In view of the foregoing amendments and remarks, it is respectfully submitted that the application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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